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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,957	02/09/2001	Kristi D. Snell	MBX 038	7578

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EXAMINER	
BAUM, STUART F	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,957	SNELL, KRISTI D.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-15,18 and 20-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-15,18 and 20-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/12/2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

DETAILED ACTION

1. The amendment filed 6/10/2004 has been entered.

2. Claims 1, 6-15, 18, 20-29 are pending and examined in the present office action.

3. The text of those sections of Title 35, U.S. Code not included in this office action can be found in a prior office action.

4. Rejections and objections not set forth below are withdrawn.

Scope of Enablement

5. Claims 1, 6-15, 18, 20-29 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA construct, or a method for expressing multiple genes in cells comprising transforming the cells with a DNA construct, comprising a single promoter at the 5' end of the construct, multiple genes or exteins encoding one or more proteins, a modified *Pyrococcus* species GB-D DNA polymerase intein fused to the carboxy-terminus portion of each gene except the last gene to be expressed and a transcription termination sequence wherein the intein sequence catalyzes excision of the exteins and wherein the excised exteins are not ligated, and wherein the DNA construct encodes a glycine or alanine linking the intein and extein amino acid sequences, does not reasonably provide enablement for a DNA construct, or a method for expressing multiple genes in cells comprising a DNA construct comprising any intein sequence from any organism operably linked within the DNA construct as specified above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

commensurate in scope with these claims. This rejection is maintained for the reasons of record set forth in the Official action mailed 3/9/2004. Applicant's arguments filed 6/10/2004 have been fully considered but they are not persuasive.

Applicants contend that the specification teaches how to make the DNA constructs that are claimed in claim 1. Applicants also contend that the specification also teaches intein sequences that prevent ligation of the cleaved exteins, see pages 7-8 of the specification (page 10, 1st paragraph).

The office contends that Applicants' claims are drawn to any intein sequence that can catalyze excision of the exteins and wherein the excised exteins are not ligated, but Applicants have only taught one intein sequence that can perform the claimed function. Applicants disclose an intein sequence from *Pyrococcus* in which serine 538 has been mutated to alanine or glycine (paragraph bridging pages 18-19). The office contends that pages 7-8 of the specification teach intein sequences in which the endonuclease domain is not present. It is not clear what is the nexus between an intein sequence not containing an endonuclease domain and an intein sequence which catalyzes excision of an exteins but which prevents ligation.

Applicants contend undue experimentation would not be required by one skilled in the art to make the claimed invention. Applicants contend that the specification contains sufficient direction and guidance. Applicant contends that the process of making DNA constructs and which sequences to use is described on pages 4-12 of the specification and in Example 1 (page 10, 2nd paragraph).

The Office contends that Applicants' claims are drawn to any intein sequence that can catalyze the excision of any exteins and wherein the excised exteins are not ligated. Applicants'

specification only discloses one intein sequence from *Pyrococcus* in which serine 538 has been mutated to alanine or glycine and which said intein performs the claimed function. Applicants have not disclosed how any intein sequence can perform as is claimed. Without such teaching, it would require undue trial and error experimentation for one skilled in the art to screen through all the possible intein sequences and to find one that can catalyze the excision of any exteins and wherein the excised exteins are not ligated.

Applicants contend that conserved amino acids have been found at intein and extein splicing points and that intein sequences are well known and cataloged on the web. Applicants contend that the disclosure teaches that mutagenesis of the C-terminal extein junction in *Pyroccoccus* species GB-DNA polymerase intein and in the *Mycobacterium xenopi* Gyra intein produces altered splicing elements that induce cleavage of the polyproteins but prevent subsequent ligation of the exteins (page 11, 1st paragraph).

The Office contends that Applicants have only taught the modified intein sequence from *Pyroccoccus* species GB-DNA polymerase that functions as claimed. Applicants disclose that the *Mycobacterium xenopi* Gyra intein should function as claimed, but have not presented any data. Applicants are invited to submit a 1.132 declaration with experimental results. In addition, Applicants claims are drawn to any intein sequence that can catalyze the excision of any exteins and wherein the excised exteins are not ligated, but Applicants have disclosed an intein sequence which has been modified from its natural state. Applicants have not disclosed any unmodified intein sequence that functions as is claimed.

Written Description

6. Claims 1, 6-15, 18, 20-29 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record set forth in the Official action mailed 3/9/2004. Applicant's arguments filed 6/10/2004 have been fully considered but they are not persuasive.

Applicants contend that the claims are directed to "modified intein sequences" (page 13, 1st full paragraph).

The Office contends that Applicants are arguing limitations not specified in the claims. Applicants' claims are drawn to any intein sequence which encompasses both modified and non-modified intein sequences. Applicants' arguments are not commensurate in scope with the claimed invention and although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants contend that inteins that prevent ligation of cleaved exteins are described. Applicants contend that the intein from *Mycobacterium xenopi* Gyra and inteins modified by mutating serine 538 to alanine or glycine are described (page 13, 1st full paragraph).

The Office contends that Applicants have only described the *Pyroccoccus* species GB-DNA polymerase intein in which serine 538 has been mutated to alanine or glycine. Applicants have not disclosed a correlation between structure and function which includes disclosing essential regions of intein sequences that are required for an intein to function properly. In

addition, Applicants have not disclosed a representative number of intein sequences that can be modified to perform the claimed function.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 8, 10-11, 15, 20, 22, and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu (A) (1996, The EMBO Journal 15(19):5146-5153; listed in IDS) in view of Xu (B) (1993 Cell 75:1371-1377) and further in view of Ingelbrecht et al (1989, The Plant Cell, 1:671-680).

The claims are drawn to a DNA construct, or a method for expressing multiple genes in cells comprising a DNA construct, comprising a single promoter at the 5' end, multiple genes or exteins encoding one or more proteins, one or more intein sequences, and transcription termination sequences, wherein at least one of the intein sequences can catalyze excision of the exteins and wherein the excised exteins are not ligated, or wherein the DNA construct encodes a glycine or alanine linking the intein and extein amino acid sequences.

Xu (A) teach a DNA construct comprising exteins and inteins, and a method for expressing exteins from the DNA construct in cells, wherein changing the codon of Ser538 to an alanine cause the two proteins to be excised but not ligated together (page 5148, Table II). Although Xu (A) does not explicitly teach all the elements of the DNA construct, Xu (A) teaches

that the construct is modified by the point mutation from the construct previously disclosed in Xu (B) (paragraph spanning 5152-5153), and hence all the elements of the construct of Xu (B) are inherently taught in Xu (A). Xu (B) teaches that the construct comprises a nucleic acid sequence encoding the Pyrococcus GB-D DNA polymerase intein operably associated at the 3' end of the nucleic acid encoding the maltose binding protein and with a nucleic acid sequence encoding the paramyosin delta-Sal operably associated at its 3'end with the Pyrococcus GB-D DNA polymerase intein (page 1371, right-hand column, first paragraph of results). Xu (B) also teach an isopropyl beta-D-thiogalactoside inducible promoter operably linked to the above nucleic acid sequence encoding the maltose binding protein::Pyrococcus GB-D-polymerase intein::paramyosin delta-Sal polypeptide (page 1376, left hand column, second paragaph).

Xu (A) in view of Xu (B) do not explicitly teach a 3' termination sequence comprising a polyadenylation signal following the last coding sequence.

Ingelbrecht et al teach plant cells transformed with DNA constructs comprising a 3' termination sequence comprising a polyadenylation signal following the last coding sequence had detectable levels of expressed nptII transcripts wherein constructs not comprising a 3' termination sequence comprising a polyadenylation signal did not exhibit expressed nptII transcripts (page 672, paragraph bridging the left and right columns).

Given the DNA construct of Xu (A) comprising exteins and inteins, and a method for expressing exteins from the DNA construct in cells, wherein modification of Ser538 to an alanine causes the exteins or proteins to be excised but not to ligated, it would have been obvious to include a 3' termination sequence comprising a polyadenylation signal following the last coding sequence as taught by Ingelbrecht et al because Ingelbrecht et al teach DNA constructs

not comprising said termination sequence did not produce mRNA transcripts in transformed cells.

Thus the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Stuart F. Baum Ph.D.
Patent Examiner
Art Unit 1638
August 19, 2004

ELIZABETH MCELWAIN
PRIMARY EXAMINER